Inclusive Separation of Acetophenone from Petrochemical By-Product with 1-Phenylethanol via Noncovalent Interactions

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Separation of the barely studied mixture of acetophenone and 1-phenylethanol, a typical by-product obtained by oil refinery plant, based on the preferential affinity of β-cyclodextrin (abbreviated as β-CD) for acetophenone is focused. To demonstrate the potential application of β-CD for separation of acetophenone from 1-phenylethanol, the noncovalent interactions of β-CD with acetophenone and 1-phenylethanol were compared from thermodynamic and conformational points of view. For the purpose of separation, a multicomponent coprecipitation technique has been established based on the selective noncovalent binding property of β-CD, which has been proved rigorously. Under the optimized conditions, the acetophenone/1-phenylethanol equimolar binary mixture can be separated with a separation factor >37. For the petrochemical by-product, which contains 74.93 wt % of acetophenone, 17.79 wt % of 1-phenylethanol, and other minor compounds, expanding the separation scale, content of acetophenone in complex can get 99.2%, and the separation efficiency of β-CD kept stable after recycling twice. *AIChE J*, 60: 2962–2975, 2014
Keywords: cyclodextrin, inclusive separation, acetophenone, 1-phenylethanol, noncovalent interaction

Introduction

Acetophenone is a raw material for the synthesis of many pharmaceuticals,[1,2] being also used to create fragrances that resemble almond, cherry, honeysuckle, jasmine, and strawberry and occurs naturally in many foods including apple, apricot, banana, and beef.[3,4] Acetophenone is also a typical substance for asymmetric transfer hydrogenation of ketones, with the product of chiral 1-phenylethanol, which is used widely in the pharmaceutical and perfume industries.[5,6] Interestingly, acetophenone can be formed through the oxidation reaction of 1-phenylethanol,[7] viz. acetophenone, and 1-phenylethanol can convert into each other through redox processes.[8] Unfortunately, as their melting points are nearly equal (about 293 K) and the boiling point of 1-phenyethanol (477 K) is slightly higher than acetophenone (475 K), the separation of them by regular distillation or crystallization is barely feasible.[9] Therefore, in the technological way of producing pure acetophenone or 1-phenylethanol, the downstream process such as separation of products and substances is one of the most challenging issues in the chemical industry. Selective adsorption on specific solid adsorbents offers promising perspectives for the design of technologically and economically efficient separation procedures. A recent study took acetophenone and 1-phenylethanol as a pair of model compounds for studying the selective adsorption of aldehyde and alcohol from the simulated biocatalytic reaction mixture with natural kerolite clay. The studied adsorbent material provided a distinct selectivity toward acetophenone as it adsorbed preferentially ketone rather than alcohol in aqueous solution.[10] Frustratingly, although it can discriminate between acetophenone and 1-phenylethanol by adsorption process, less attention has so far been paid to the separation of them compared to the hottest mixture systems such as C_8-isomers, *cis*-, and *trans*-olefins and enantiomers, and so forth.[11–19]

Acetophenone and 1-phenylethanol not only coexist with other impurities in the redox reaction mixtures, but also commonly coexist with appreciable amounts in petrochemical by-products as well as in petroleum effluent.[20] For instance, the processes of epoxidation of ethylbenzene as well as synthesis of styrene usually produce by-products, mainly containing acetophenone and 1-phenylethanol.[21–23] Take Sinopec Zhenhai Refining & Chemical Company (Abbreviated as ZRCC), for example, the propylene oxide/styrene monomer coproduction (PO/SM) plant can yield certain amount of by-product, which contains 74.93 wt % of acetophenone, 17.79 wt % of 1-phenylethanol, 2.45 wt % of benzyl alcohol, 0.54 wt % of propylene glycol, 0.31 wt % of styrene, and other compounds in trace amount. Economic considerations favor recovering acetophenone and 1-phenylethanol from this by-product. Unfortunately, how to recover the main compounds from this by-product remains a problem. It is found impossible to convert them to each other through catalytic redox reactions, as the catalysts are usually vulnerable to other impurities, which coexist in the mixture. There is, therefore, an urgent need to develop a novel method to selectively recover acetophenone or 1-phenylethanol from the mixture.

Cyclodextrins (CDs), cyclic oligosaccharides commonly composed of six, seven, or eight (α, β, and γ-CD,

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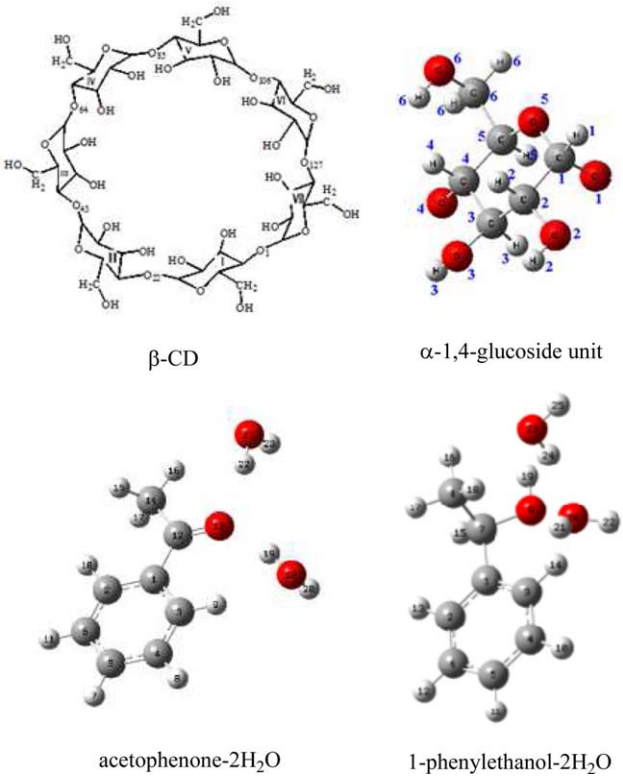

Figure 1. Molecular structures optimized by PM3 and atom number of β-CD, glucose unit connected via α-1,4 bonds and hydrates of substrates with two H_2O_s.

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respectively) glucose units, possess the attractive ability of binding a wide variety of substances into their hydrophobic cavities forming host–guest inclusion complexes.[24–26] This property has led to their extensive applications in many areas of science and technology to serve as artificial enzymes for biological mimicking.[27] One of the most interesting applications is inclusive separation, which is obtained by a difference in reversibly noncovalent interaction of compounds with CDs, whereby Van der Waals force, hydrogen bonding as well as hydrophobic interaction can be the driving forces.[28,29] Among CD homologues, β-CD is generally the most useful for its appropriately sized cavity, accessibility, and lowest cost. In addition, in the β-CD molecule (Figure 1), a complete secondary belt can be formed by the H-bonds, which jointed by the 2C—OH group of one glucoside unit and the 3C—OH group of the adjacent glucoside unit, and the entire β-CD molecule possesses a rather rigid structure.[30] This intramolecular H-bond formation causes that β-CD has the lowest water solubility among all CDs.[31] The water solubility of β-CD is low (1.85 g/100 mL) at room temperature and shows a normal temperature dependence,[32] ensuring that β-CD can be used conveniently for a direct inclusive separation system. Up until now, β-CD has been increasingly used to separate *cis*-, and *trans*-isomers, positional isomers, and so forth.[33,34]

In this study, it was found that β-CD exhibits preferential inclusion for acetophenone over 1-phenylethanol as a result of the selective recognition of the β-CD cavity. Therefore, it may be a kind of resource-saving innovation for nonrenewable resources, if pure acetophenone or 1-phenylethanol could be recovered from these by-products through inclusive separation method. This study demonstrated the rational use of noncovalent interactions between β-CD and guests for separating acetophenone from mixture with 1-phenylethanol. On the experimental front, a vast effort has been invested to study the process that governs the formation of the complexes. Quantum mechanics calculations provide atomic-level insight into possible inclusion geometries and thereby the relative stabilities of complexes. The calculated binding energies are consistent with the experimentally obtained binding constants measured by UV–Vis. In addition, the thermodynamic parameters of binding process were then determined by isothermal titration microcalorimetry measurements, and the geometries of β-CD complexes were investigated by the NMR spectroscopy and X-ray diffraction (XRD).

For the purpose of separation, a multicomponent coprecipitation technique in the presence of saturated aqueous solution of β-CD was used, and the experimental parameters were investigated in sequence. In the optimum condition, the inclusive separation of binary mixtures with different molar compositions has been conducted. Moreover, the selective inclusion of acetophenone from petrochemical by-product (ZRCC) was tested in bench-scale. To be useful to field practitioners, advances in separation research must be capable of being scaled up from the laboratory to the field. The scale of inclusive separation procedure varied between bench-scale and 50× bench-scale for selective inclusion of acetophenone from petrochemical oil. The stability of the scale-up system is promising for further industrial scale-up. It was found that this inclusive method can yield nearly four times higher separation efficiencies than the adsorptive method reported previously.[10] Compared with the conventional liquid–liquid extraction, a decreasing demand for organic solvents was also expected in the industrial application of inclusive separation by β-CD. Moreover, β-CD is commercially available at a low cost and can be easily regenerated with stable cyclic performance, allowing a more efficient and economical separation process.

To our knowledge, no similar studies on inclusive separation of acetophenone and 1-phenylethanol mixtures by β-CD have been performed. We believe that our current approach will provide a novel convenient method for efficient separation of acetophenone and 1-phenylethanol, even being suitable for separation of the other aromatic aldehydes and alcohols.

Experimental

Chemical

β-CD (>99%) was purchased from Shanghai Boao Biotechnology Co., China. Acetophenone (≥99.5%, GC) was obtained from Shanghai Lingfeng Chemical Reagent Co., China, and 1-phenylethanol (>98%, GC) was the product of TCI, Japan. Ethyl acetate (≥99.9%) was provided by Guangzhou Chemical Reagent Co., China. Naphthalene (≥99.9%) is purchased from Damao Chemical Reagent Co. The petrochemical by-product was provided from Sinopec ZRCC.

Measurement of binding constants

The measurement of binding constants of β-CD and the guests was realized by spectrophotometric analysis with UV–Vis spectrophotometry (UV-2450, Shimadzu, Japan) at the maximum absorption wavelength (λ_{max}). The value of

λ_{max} was 245.4 nm for acetophenone and 206.0 nm for 1-phenylethanol. The concentrations of the guests in sample solutions were kept constant at about 0.1 mmol/L, while the concentration of β-CD varied between 0 and 10 mmol/L in order to determine the binding constants of β-CD to the guests. All sample solutions to be detected were prepared by mixing β-CD with a guest in water and kept oscillating at 298 K for 6 h before taking the measurements. Assuming a 1:1 stoichiometry of complex formation between guest molecule and β-CD, the binding constant (K) can be obtained using the Benesi–Hildebrand equation[35,36]

$$\frac{1}{\Delta A} = \frac{1}{K[\mathrm{G}]_0 \Delta\varepsilon} \cdot \frac{1}{[\mathrm{CD}]_0} + \frac{1}{[\mathrm{G}]_0 \Delta\varepsilon} \tag{1}$$

where, K (L/mol) is the binding constant for the formation of β-CD inclusion complex, ΔA is the difference between the absorbance per centimeter of free and complexed guest at λ_{max}, $\Delta\varepsilon$ is the difference between molar absorbance coefficients of free and complexed guest. $[G]_0$ (mmol/L) is the initial concentration of guest, $[CD]_0$ (mmol/L) is the initial concentration of β-CD. Hence, plotting $1/\Delta A$ versus $1/[CD]_0$ gives a slope of $1/(K \cdot \Delta\varepsilon \cdot [G]_0)$ and an intercept of $1/([G]_0 \cdot \Delta\varepsilon)$. The ratio of the intercept to the slope can be taken as an estimation of the binding constant K.

Microcalorimetric measurements

Calorimetric titrations were performed in duplicate with a VP-ITC Microcalorimeter (Microcal Co.) at 288, 298, and 308 K in aqueous solution. All solutions were degassed and thermostated using a Thermo Vac accessory before titration experiment. Each titration experiment consisted of 18 successive injections of 15 μL of β-CD aqueous solution (10 mmol/L) from syringe into the sample cell charged with 1.44 mL of guest aqueous solution (1 mmol/L), with time intervals of 300 s. A control experiment was performed to determine the heat of dilution by injecting a β-CD solution into water. The dilution enthalpy was subtracted from the apparent enthalpy obtained in each titration run, and the net reaction enthalpy was analyzed using the "one set for sites" binding model by Microcal Origin 5.0 for isothermal titration calorimetry (ITC). We assumed binding ratio as 1:1 and fixed it upon fitting process. The affinity constant (K_a, dimensionless) and change in enthalpy (ΔH, kJ/mol) were the floating parameters of the fit. From these results, the Gibbs free energy change (ΔG, kJ/mol) and the entropic change [ΔS, J/(mol·K)] were also deduced according to Eq. [237]

$$\Delta G = -RT \ln K_a = \Delta H - T\Delta S \tag{2}$$

Preparation of complexes and geometry characterization

The complex of β-CD with acetophenone or 1-phenylethanol for NMR and XRD analysis was prepared with conventional suspension method.[38] β-CD (1.135 g) was dissolved in 50 mL of water, and then 0.120 g of acetophenone or 0.122 g of 1-phenylethanol was added to the aqueous solution. Kept at 343 K under magnetic stirring for 6 h, the reaction mixture was cooled at 277 K overnight and a white precipitate was obtained. The precipitate was filtered and washed by n-hexane in order to remove the untrapped acetophenone or 1-phenylethanol. The resulting solid inclusion complex was dried overnight at 303 K under high vacuum.

The two-dimensional rotating frame nuclear overhauser effect spectroscopy (2D ROESY) experiment was performed on a Bruker WM400 spectrometer at 400 MHz, using D_2O as solvent at 298 K. Solid-state ^{13}C CP/MAS NMR spectra were recorded at 125.72 MHz on a Varian Inova-500 NB spectrometer (at ambient temperature), with an optimized $\pi/2$ pulse for ^1H of 4.5 μs, 2 ms contact time, a spinning rate of 7 kHz, and 12 s recycle delays. The chemical shifts were quoted in parts per million from the external standard tetramethylsilane. The XRD patterns were measured on a Rigaku D/MAX 2200 (Tokyo, Japan) instrument with Cu Kα radiation at a scanning speed of 4°/min. Complex samples were mounted on a sample holder and scanned with a step size of $2\theta = 0.02°$ between $2\theta = 5°$ and 50°.

Separation of the binary mixture of acetophenone and 1-phenylethanol

Separation was studied by coprecipitation technique in a batch mode of operations. A typical separation procedure was taken as follows: β-CD saturated aqueous solution was prepared by dissolving 1.135 g of β-CD (1 mmol) in 25 mL of water at 318 K. The equimolar mixture of acetophenone and 1-phenylethanol (4 mmol) was then added dropwise to the saturated solution of β-CD, while continually being incubated in a water bath at 318 K for 2 h. Interestingly, white precipitate of inclusion complex appeared soon after mixing the β-CD solution and guests, indicating that the guest molecule was embraced into the cavity of β-CD to form an inclusion complex and the solubility of β-CD complex decreased dramatically. The aqueous suspension was stored at room temperature for 12 h followed by vacuum filtration enabled the complete isolation of the binding complexes in the form of white precipitate. To dissociate the inclusion complex, 10 mL of ethyl acetate was poured into the complex precipitate, followed by being stirred for 30 min. Then, the guest species were released from β-CD powder, being dissolved in eluate. Conversely, guests in residue solution can be extracted with the same volume of ethyl acetate. The eluate of complex and the extract from residue solution were analyzed by gas chromatography (Shimazu GC-14C unit) equipped with flame ionization detector using a FFAP column (50 m × 0.25 mm × 0.33 μm). The content of acetophenone and 1-phenylethanol were calculated by internal standard method using naphthalene as internal standard. The measurement conditions were as follows: nitrogen was used as carrier gas, detector temperature, 523 K; column temperature, 443 K. Under these conditions, the retention times were 11.04 min for acetophenone, 14.08 min for naphathelene, and 14.90 min for 1-phenylethanol, respectively. The separation factor (dimensionless) is defined from Eq. 3 as the ratio between the quotient of the complex molar amounts and the quotient of the residue molar amounts[39]

$$\text{Separation factor} = \frac{n_{\text{acetophenone, c}} \,/\, n_{\text{1-phenylethanol, c}}}{n_{\text{acetophenone, r}} \,/\, n_{\text{1-phenylethanol, r}}} \tag{3}$$

where, $n_{\text{acetophenone, c}}$ (mmol) and $n_{\text{1-phenylethanol, c}}$ (mmol) are the molar amounts of acetophenone and 1-phenylethanol in complex, $n_{\text{acetophenone, r}}$ (mmol) and $n_{\text{1-phenylethanol, r}}$ (mmol) are the molar amounts of acetophenone and 1-phenylethanol in residue solution.

For investigation of effects of experimental parameters on the separation efficiency, equimolar mixture of acetophenone and 1-phenylethanol was used as substance, and the effects of molar ratio of guest/β-CD, binding temperature, binding

time, and precipitating time were investigated in sequence. At the beginning, the effect of guest/β-CD molar ratio was investigated on changing the guest/β-CD molar ratio, while the other experimental parameters were fixed as: binding temperature 318 K, binding time 6 h, precipitating time 24 h, and the molar ratio of guest/β-CD varied from 1/1 to 6/1. It would be noted that the inclusion experiment was conducted in saturated β-CD solution as mentioned earlier, and the solubility of β-CD in water shows a normal temperature dependence. Therefore, while the binding temperature was investigated at the range of 298–343 K, dissolving constant amount of β-CD in appropriate amounts of water, a series of saturated β-CD solutions as a function of temperature were obtained.

After optimization of separation conditions, the separation of binary mixtures containing various molar fraction of acetophenone was performed under optimum conditions. The initial molar fractions of acetophenone ($x_{\text{acetophenone},0}$, %) and 1-phenylethanol ($x_{\text{1-phenylethanol},0}$, %) in binary mixtures were varied from 20% to 80%. After experiment, the acetophenone molar fraction in complex ($x_{\text{acetophenone,c}}$, %) and 1-phenylethanol molar fraction in residue solution ($x_{\text{1-phenylethanol,r}}$, %) were calculated based on Eqs. 4 and 5

$$x_{\text{acetophenone,c}} = \frac{n_{\text{acetophenone,c}}}{n_{\text{acetophenone,c}} + n_{\text{1-phenylethanol,c}}} \times 100\% \quad (4)$$

$$x_{\text{1-phenylethanol,r}} = \frac{n_{\text{1-phenylethanol,r}}}{n_{\text{acetophenone,r}} + n_{\text{1-phenylethanol,r}}} \times 100\% \quad (5)$$

where, $n_{\text{acetophenone,c}}$, $n_{\text{1-phenylethanol,c}}$, $n_{\text{acetophenone,r}}$, and $n_{\text{1-phenylethanol,r}}$ were defined as above.

Selective inclusion of acetophenone from petrochemical by-product

The petrochemical by-product (abbreviated as oil), which produced in PO/SM technology of ZRCC, mainly contains acetophenone (74.93 wt %), 1-phenylethanol (17.79 wt %), and other minor components (2.45 wt % of benzyl alcohol, 0.54 wt % of propylene glycol, and 0.31 wt % of styrene, etc.). To get highly purified acetophenone from this oil, the selective inclusion experiments were conducted in laboratorial bench-scale, 10 and 50 times of bench-scale, respectively. In a typical process for the laboratorial bench-scale of selective inclusion of acetophenone from this oil, 1 g of β-CD was dissolved in 20 mL of water at 318 K, followed by the slow addition of 0.45 g of oil with stirring magnetically. The white precipitate occurred immediately as inclusion complex was formed between β-CD and guests. The suspension was kept stirred at 318 K for 2 h, followed by standing at room temperature for 12 h. The complex was separated from the suspension solution through filtration, and then dried to constant weight at room temperature. To recover the guest and to regenerate β-CD, ethyl acetate was chosen as eluent. The inclusion complex was added to 10 mL of ethyl acetate, followed by stirring magnetically at room temperature for 30 min, releasing guests from the inclusion complex. Through filtration, the regenerated β-CD was separated from the eluted solution. The regenerated β-CD was dried to constant weight at room temperature. To determine the amount of acetophenone and 1-phenylethanol in the eluted solution, GC was used, and the method was according to the conditions as aforementioned. Scale-up of selective inclusion experiments were achieved by enlarging the dosage from bench-scale to 10, 50 times of bench-scale while other conditions were remaining unchanged. In addition, three inclusion-regeneration cycles were performed in 50× bench-scale.

The mass amount of oil included in the complex ($m_{\text{oil, c}}$, g) was calculated from Eq. 6

$$m_{\text{oil,c}} = m_{\text{c}} - m_{\text{CD,R}} \quad (6)$$

where, m_{c} (g) is the weight of complex, and $m_{\text{CD, R}}$ (g) is the weight of regenerated β-CD.

And the mass fractions of acetophenone ($w_{\text{acetophenone,c}}$, %) and 1-phenylethanol ($w_{\text{1-phenylethanol,c}}$, %) in complex were calculated as in Eqs. 7 and 8

$$w_{\text{acetophenone,c}} = \frac{m_{\text{acetophenone,c}}}{m_{\text{oil,c}}} \times 100\% \quad (7)$$

$$w_{\text{1-phenylethanol,c}} = \frac{m_{\text{1-phenylethanol,c}}}{m_{\text{oil,c}}} \times 100\% \quad (8)$$

where, $m_{\text{acetophenone,c}}$ (g) and $m_{\text{1-phenylethanol,c}}$ (g) are the weights of acetophenone and 1-phenylethanol in complex, $m_{\text{oil,c}}$ (g) is the weight of oil in the complex as defined above.

Computational Methods

The initial structures of β-CD, acetophenone and 1-phenylethanol were constructed with the help of CS Chem3D Ultra and were fully optimized with PM3. To obtain accurate computational results, explicit solvation model has been used to investigate solvent effects on binding energies of inclusion complexes. Here, the explicit solvation effect was considered by placing two water molecules (H_2Os) around carbonyl group or hydroxyl of substrates to create the hydrates and was optimized with PM3 followed by ONIOM2 calculation. As shown in Figure 1, two water molecules (H_2Os) were symmetrically placed around O13 atom of acetophenone or O9 atom of 1-phenylethanol to create their dehydrates.

The coordinate system used to define the process of complexation is shown in Figure 2. The labeled carbon atom (C*) of the guest molecule is used to express the relative position between the guest and host while the guest passes through the cavity of β-CD. The process of complexation contains one passing process and one circling process. In passing process, the glycosidic oxygen atoms were placed onto the *XY* plane and their center was designated as the coordination origin, and the longer dimension of guest was placed onto the *Z* axis. The primary hydroxyl groups of β-CD were placed pointing toward the positive *Z* axis. Multiple starting positions were generated by movement of the guest molecules from $+Z$ to $-Z$ direction (complex named head down) or from $-Z$ to $+Z$ direction (complex named head up). The relative position between the guest and β-CD was measured by the *Z*-coordinate of the labeled carbon atom (C*) ranges from 9 to -7 Å at 1 Å intervals. Each complex was energy minimized in vacuo, and the lowest energy complexes were used as the starting geometries for circling process. In circling process, guest was placed in *YZ* plane and circled anticlockwisely around the *Z* axis from 0 to 360 at 20 intervals. The optimized geometries of complexes were further calculated at single point by the two-layered hybrid ONIOM2 (B3LYP/6–31G: PM3) method, in which the host molecule β-CD was submitted to the low level of quantum calculations since we assumed it provides only an environmental effect and contains the larger number of atoms while the guest molecule was treated at a high level

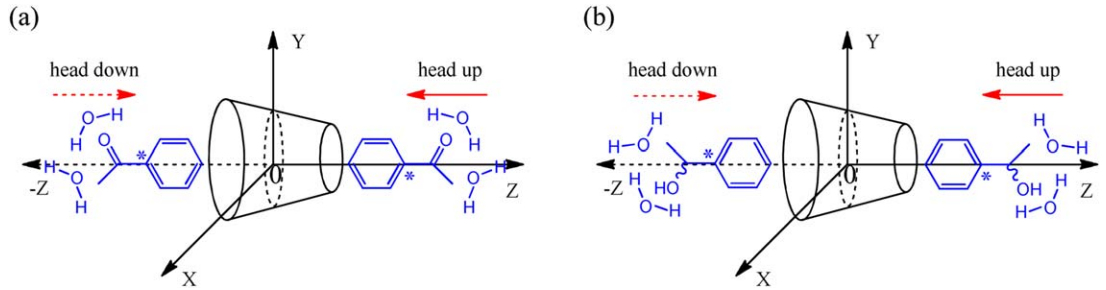

Figure 2. Coordinate systems used to follow the (1:1) β-CD complexation processes with acetophenone-2H_2O hydrate (a) and 1-phenylethanol-2H_2O hydrate (b).

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of calculation at a basis set corresponding to B3LYP/6–31G. To understand and to compare the stabilities of the studied supramolecular structures, the binding energy (ΔE_{bind}) was calculated by energetic difference between complexed form and isolated species (Eq. 9)

$$\Delta E_{bind} = E_{comp} - E_{guest} - E_{host} \quad (9)$$

where E_{comp}, E_{guest}, and E_{host} in kJ/mol represent the total energy of the complex, the free guest molecule, and the free host molecule, respectively. The magnitude of the binding energy indicates the tendency toward complexation.

All calculations were performed with the Gaussian program series 2003. CS Chem3D 10.0 and Gaussian Viewer were used as graphical medium.

Results and Discussion

Theoretical investigation of the inclusion process of acetophenone and 1-phenylethanol in β-CD

The energy changes for two opposite complexation orientations of β-CD and guests were calculated by the semiempirical PM3 method. The variation of binding energy in passing process and circling process for the two guests in vacuum was illustrated in Figure 3, respectively. Generally speaking, the more negative ΔE_{bind} is, the more thermodynamically favorable is the inclusion complex. The negative ΔE_{bind} in Figure 3 demonstrated that β-CD could interact with acetophenone hydrates and 1-phenylethanol hydrates to form stable inclusion complexes. The negative binding energy in the inclusion emulation indicated that the

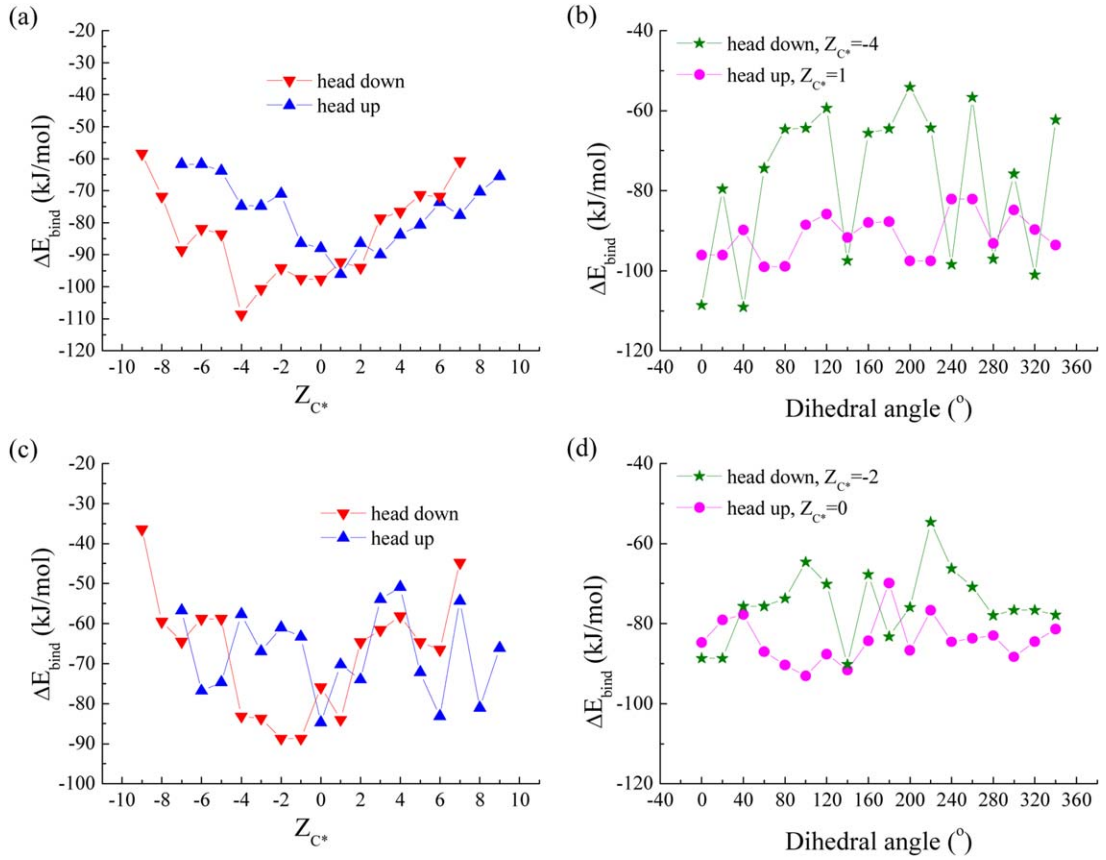

Figure 3. Energy graphs for inclusion processes of β-CD with acetophenone-2H_2O (a), (b) and 1-phenylethanol-2H_2O (c), (d) at different positions (Z_{C^*}) and dihedral angle (°).

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1. Binding Energies of β-CD/Substance-2H_2O Complexes Calculated by PM3 and ONIOM2 and the Corresponding Z_C[a] and θ

Host–guest inclusion complexes	Orientations	Z_C[a]	θ	ΔE_{bind1}[a]	ΔE_{bind2}[b]
β-CD/acetophenone-2H_2O	head down	−4	40	−109.0470	−104.9994
	head up	1	60	−99.0272	−96.3623
β-CD/1-phenylethanol-2H_2O	head down	−2	140	−90.2136	−88.6843
	head up	0	100	−93.0948	−89.2642

[a]Binding energy calculated by PM3 method.
[b]Binding energy calculated by ONIOM2 (B3LYP/6–31G (d): PM3) method.

complexes preferred to adopt inclusion geometry with the guests in order to gain more stable supramolecular interactions, such as the C—H···π interaction, hydrophobic interaction, and formation of intermolecular hydrogen bond between β-CD and the guest. In addition, it was found that head down yielded the most energetically favorable geometry for the 1:1 β-CD/acetophenone complexes. While, the most stable configuration of 1-phenylethanol hydrates is in head up, differing from acetophenone hydrates. To further verify their stabilities, the optimized structures of the most stable complexes in each orientation by the hybrid ONIOM2 method were investigated. The most stable complexes in each orientation were summarized in Table 1. As shown in Table 1, the binding energies of β-CD complexes at ONIOM2 level were a little smaller than the corresponding results of PM3. According to the results in Table 1, the Z_{C*} for the global minima were about $-4 \sim 1$ Å, which indicated that phenyl ring was completely inserted hydrophobic cavity of β-CD and H_2Os around guests were partially penetrated. The results indicate that the functional group and water molecules are located out of the β-CD cavity, is much favorable, probably, due to effective hydrophobic interactions. It is also shown that the binding energy of acetophenone hydrates with β-CD is bigger than 1-phenylethanol hydrates with β-CD, indicating the interactions of β-CD with acetophenone are stronger than those of β-CD with 1-phenylethanol.

The ONIOM2 method applies multiapproaches to simultaneously treat different parts of a system and can supply useful geometry information for the inclusion complexes. Geometries of the most stable inclusion complexes optimized by ONIOM2 (B3LYP/6–31G(d): PM3) were displayed in Figure 4. It is found that the phenyl ring of guests (especially for acetophenone hydrates) strongly deviated from Z axis, which suggested that inclusion complexes were stably formed via intermolecular weak interactions such as Van der Waals interaction, electrostatic interaction, hydrogen bond interaction, and so forth. Generally, hydrogen bond interaction is much stronger than Van der Waals interaction, and an O—H···O or C—H···O interaction often contributes a stable energy of 16–25 kJ/mol[40] or 0.7–2.8 kJ/mol[41] to binding energy. The types of hydrogen bond and their numbers, bond lengths, and bond angles were listed in Table 2. The glucose units in β-CD labeled as I $\sim$ VII, and the C, H, O in each unit were accordingly defined as 1C $\sim$ 6C, 1H $\sim$ 6H, and 2O $\sim$ 6O (as shown in Figure 1). Two types of hydrogen bond interactions, for example, O—H···O and C—H···O have been considered. From the results in Table 2, it is found that bond lengths for O—H···O and C—H···O hydrogen bonds varied from 2.6987 to 3.2302 Å and from 3.2942 to 3.4418 Å, and the corresponding bond angles ranged from 134.64 to 161.87° and from 103.93 to 142.81°, respectively. The stronger hydrogen bond interactions for β-CD/acetophenone hydrates complex than β-CD/1-phenylethanol hydrates complex can also be inferred from the numbers and strengths of hydrogen bond listed in Table 2, leading to different stabilities of complexes.

Binding constant with β-*CD*

The UV absorption spectra of the solution of complexes with different concentrations of β-CD are shown in Figure 5. The initial concentrations of acetophenone and 1-phenylethanol are kept at 8.27×10^{-2} mmol/L and 0.1184 mmol/L, respectively, while the concentration of β-CD is in the range from 0 to 10 mmol/L. It was found that the absorbance of solution decreased with the increase of β-CD concentration, which resulted from the more rigid structure formed by guest molecules entrapped in cavity of β-CD.

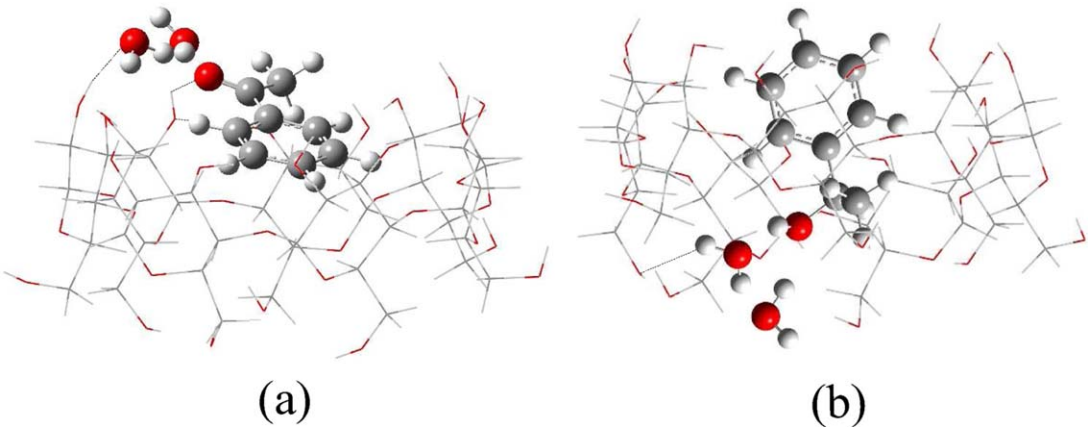

Figure 4. Optimized structure of β-CD inclusion complexes with acetophenone hydrates (a) and 1-phenylethanol hydrates (b) obtained by ONIOM2 (B3LYP/6–31G(d):PM3) method.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 2. Number, Type, Bond Length (r), and Bond Angle (A) of Intermolecular Hydrogen Bond Between Hydrates and β-CD Calculated by ONIOM2(B3LYP/6–31G(d):PM3)

Inclusion complexes	Number	Type	r (Å)	A (°)
β-CD/acetophenone-2H_2O	5	C5—H7 ··· 4O(VII)	3.2942	130.98
		C14—H17 ··· 3O(VI)	3.1369	103.93
		O18 ··· 3H—3O(III)	2.7194	161.87
		O21 ··· 3H—3O(II)	2.6987	160.14
		O21—H20 ··· 2O(II)	2.7156	149.56
β-CD/1-phenylethanol-2H_2O	3	C3—H9 ··· 4O(II)	3.3631	125.18
		C4—10H ··· 2O(II)	3.4418	142.81
		O20—H20 ··· 6O(III)	3.2302	134.64

Two double reciprocal Benesi–Hildebrand plot, that is, plot of $1/\Delta A$ versus $1/[CD]_0$ were constructed and are shown in Figure 6. The obtained linear correlations (R^2) for the curves are 0.9937 (acetophenone) and 0.9855 (1-phenylethanol), indicating that acetophenone and 1-phenylethanol both form 1:1 inclusion complexes with β-CD. The K values of inclusion complexes of β-CD/acetophenone and β-CD/1-phenylethanol obtained from absorption spectroscopy at 298 K were calculated. The association ability of acetophenone with β-CD (356.68 L/mol) is obvious higher than that of 1-phenylethanol (138.81 L/mol). Furthermore, based on the procedure for determination of solubility in water as described previously, solubility of guest in water at 298 K was determined.[42] It was found that the saturated concentrations of acetophenone and 1-phenylethanol in water at 298 K were 65.76 and 160.87 mmol/L, respectively. It is noteworthy that the extraordinarily strong hydrophobic interaction may contribute to the more stable complex between β-CD and acetophenone than 1-phenylethanol.

Thermodynamics Parameters

After validation of the 1:1 complexation stoichiometry, the ITC experiment was used to investigate the interaction between β-CD and different guests, which provides more information about the thermodynamic parameters of the complexation process. ITC measurements were performed by injecting β-CD to guests solutions, and the corresponding heat flows were recorded as a function of time, as shown in the top of Figures 7b,d. The occurrence of a binding event was revealed by the presence of exothermic peaks following each injection. However, the positive heat effects of dilution as shown in Figures 7a,c indicated the β-CD dilution is an endothermic process. As shown in Figures 7a,c, in the presence of acetophenone, the titration curve of acetophenone assumes higher exothermic values (more negative) than that of 1-phenylethanol, demonstrating the stronger host–guest interaction between β-CD and acetophenone than 1-phenylethanol.

The thermodynamic parameters collected in Table 3 indicated that the complexation of the two guests with β-CD was driven in a thermodynamically favorable way with negative enthalpy and positive entropy change. The enthalpy changes could be attributed to the binding of the high enthalpy-rich water molecules released from the β-CD cavity with the bulk water molecules, as well as to the Van der Waals and hydrogen bond interactions between host and guest molecules. Conversely, the release of water molecules that were originally residing within the cavity and the induced dehydration of peripheral hydroxyl groups of β-CD appear to be jointly responsible for an intrinsic entropy gain. Although the binding process results from favorable contributions from both enthalpy and entropy, it can be found obviously from Table 3 that the enthalpy changes are not only the main contribution to the binding process ($-\Delta H > T\Delta S$) but also the determining factor for the binding abilities. In addition, Gibbs energy changes for the binding processes of β-CD with acetophenone are always more negative than those for the binding processes of β-CD with 1-phenylethanol at various temperatures, indicating that β-CD prefers to bind with acetophenone than 1-phenylethanol. Temperature increase results in more negative ΔH, whereas the decrease of ΔS was observed, indicating higher temperature may provide more chances for guest molecules to pass the external boundary layer. While ΔH and ΔS show systematic changes with the increase in temperature, ΔG does not

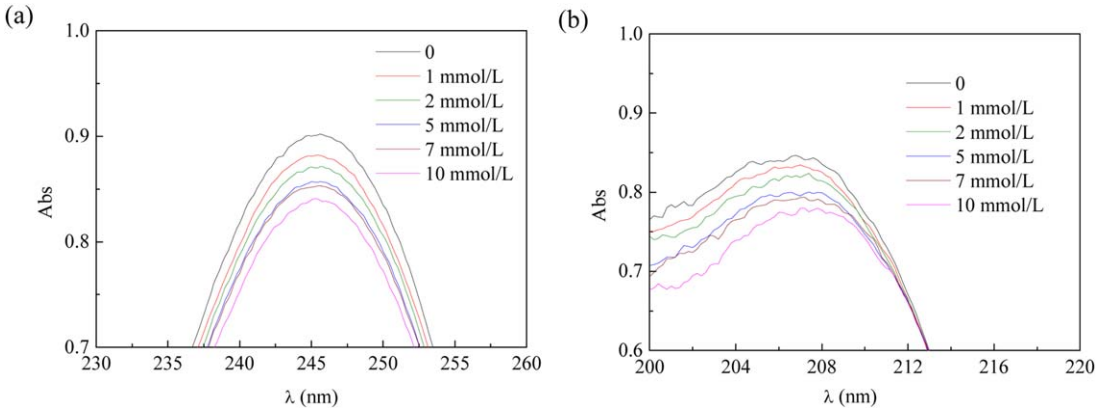

Figure 5. Enlarged view of UV absorption spectra of (a) acetophenone ($[G]_0 = 8.27 \times 10^{-2}$ mmol/L) and (b) 1-phenylethanol ($[G]_0 = 0.1184$ mmol/L) at different concentration of β-CD solution ($[CD]_0 = 0$–10 mmol/L).

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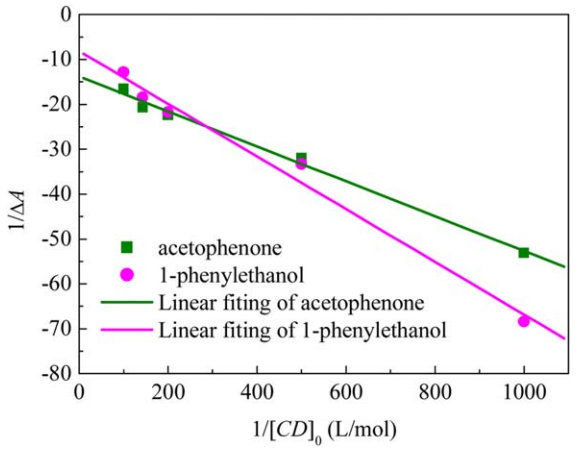

Figure 6. Plots of $1/\Delta A$ versus $1/[CD]_0$.

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show systematic changes. For instance, a fluctuation of ΔG for acetophenone and β-CD with the temperature was observed. As listed in Eq. 2, ΔG mainly depends on the affinity constant K_a and temperature T, exhibiting an increasing trend as a function of these parameters. Therefore, this fluctuation may be attributed to the trends (increase first, then decrease) of K_a caused by temperature variation. Furthermore, the simulated affinity constants K_a for the two guests are lower than the binding constant K obtained by spectrum measurements. Such deviation may be connected with the quite weak interaction between guests and β-CD in solution as well as the assumption made in fitting procedure in microcalorimetric titration, and the obtained results are only apparent values of the complexation process.[43,44]

Geometry of β-CD inclusion complexes

To investigate the inclusion geometry of β-CD with acetophenone and 1-phenylethanol, ^{1}H 2D NMR, ^{13}C CP/MAS NMR and XRD which have become important tools for the characterization of β-CD inclusion complexes, were used in sequence. The atom numbers of host and guest molecules are defined according to Figure 1. More specifically, the carbon and hydrogen atoms in glucose unit of β-CD and the aromatic hydrogen atoms of acetophenone and 1-phenylethanol molecule were accordingly defined as 1C $\sim$ 6C, 1H $\sim$ 6H, H7 $\sim$ H11, and H10 $\sim$ H14, respectively.

In ROESY spectrum, the presence of NOE cross-peaks between protons from both species indicates separations closer than 0.4 nm in space,[45] and the relative intensities of cross-peaks depend on the distance between the corresponding protons. As seen in Figures 8a,c, the 2D ROESY spectra of β-CD/acetophenone and β-CD/1-phenylethanol complexes, in which the intermolecular cross-peaks between guests hydrogens with the internal or external protons of β-CD can be seen. In addition, the dipolar correlations between aromatic hydrogen atoms of guests and internal protons of β-CD are better observed in expansion spectra (Figures 8b,d).

As seen from Figures 8a,b, the cross-peaks between the interior 3H, 5H, and 6H protons of β-CD cavity and the phenyl ring protons H9—H10 (strong), H8—H11 (medium), and H7 (weak) of acetophenone were clearly observed in the ROESY spectrum, implying that the phenyl ring of acetophenone molecule was deeply located in the β-CD cavity. From Figure 8a, it can be seen a weak cross-peak between methyl protons of acetopheone (2.5 ppm) with 6H protons of β-CD cavity. Therefore, the hypothesis that carbonyl group of acetopheone is close to the primary face of β-CD can be considered. Instead, the ROESY spectra in Figures 8c,d revealed that the signals of 1-phenylethanol phenyl ring correlated with H3, H5 protons of β-CD are so weak, distinctly indicating that 1-phenylethanol was shallowly included at cavity of β-CD to some extent. The spatial conformations of these two complexes were further confirmed by ^{13}C CP/MAS NMR and XRD as described below.

Figure 9 shows the ^{13}C CP/MAS NMR spectra of pure β-CD hydrate and the resulting two inclusion complexes. The spectrum of β-CD is similar to that previously reported and exhibits multiple resonances for each type of carbon atom.[46] This has been mainly correlated with different torsion angles about the 1–4 linkages for 1C and 4C, and with torsion angles describing the orientation of the hydroxyl groups. The different carbon resonances are assigned to 1C (101–104 ppm), 4C (78–84 ppm), 2C, 3C, 5C (71–76 ppm), and 6C (57–65 ppm). By contrast, the corresponding β-CD carbons for the inclusion complexes are generally observed mainly as single broad peaks centered around 104, 82, 73, and 61 ppm, respectively. This can tentatively be attributed to complexation, assuming that inclusion of guest molecules in the β-CD cavities will be accompanied by the host molecule adopting a more symmetrical conformation, with each glucose unit in a similar environment. In addition to the resonances for the β-CD carbons, the spectra of inclusion complexes exhibit several relatively weak, broad lines that can be assigned to the carbon atoms of the guest molecules. The β-CD/acetopheone complex contains additional low-intensity peaks at about 128 and 26 ppm, attributed to the phenyl carbon atoms and methyl carbon atom. Compared to the former, there are two similar weaker peaks at 127 and 129 ppm in the spectrum of β-CD/1-phenylethanol complex, which attributed to the phenyl carbon atoms at different sites.

XRD patterns collected of β-CD complexes indicated a partial conversion from columnar to cage crystal structure. It is known that β-CD inclusion compounds usually crystallise from water to give "channel" or "cage" structures in which the β-CD molecules are stacked like coins in a roll or arranged in a herring-bone pattern.[47] The XRD patterns of β-CD and its inclusion complexes with acetophenone and 1-phenylethanol are shown in Figure 10. Acetophenone and 1-phenylethanol are liquid at room temperature, so there are no XRD data available. The powder XRD pattern of complex is very distinct from the pattern of pure β-CD hydrate, suggesting the formation of a new phase corresponding to a new inclusion complex. β-CD has the strongest peak at 12.6°, but the peak is shifted to lower 2θ value for β-CD/acetophenone and β-CD/1-phenylethanol complexes because of the enlarged lattice spacings of the complex. Free β-CD in the low angle range of 5.0 $\sim$ 10.0° has a strong sharp peak and a very weak peak at 2θ values of 9.0° and 6.1°, respectively. However, the peak at 9.1° in free β-CD disappears completely in complexes, and there are three peaks at 6.1°, 7.3°, and 9.9°. In addition, the peaks of 14.6°, 15.5°, 17.4°, and 19.0° of complexes are much stronger than the free β-CD. The above results suggest that there is an intermolecular interaction in solid state between β-CD and the two guests. In addition, the two kinds of complexes gave out similar XRD patterns, demonstrating the guests have already been bound to β-CD.

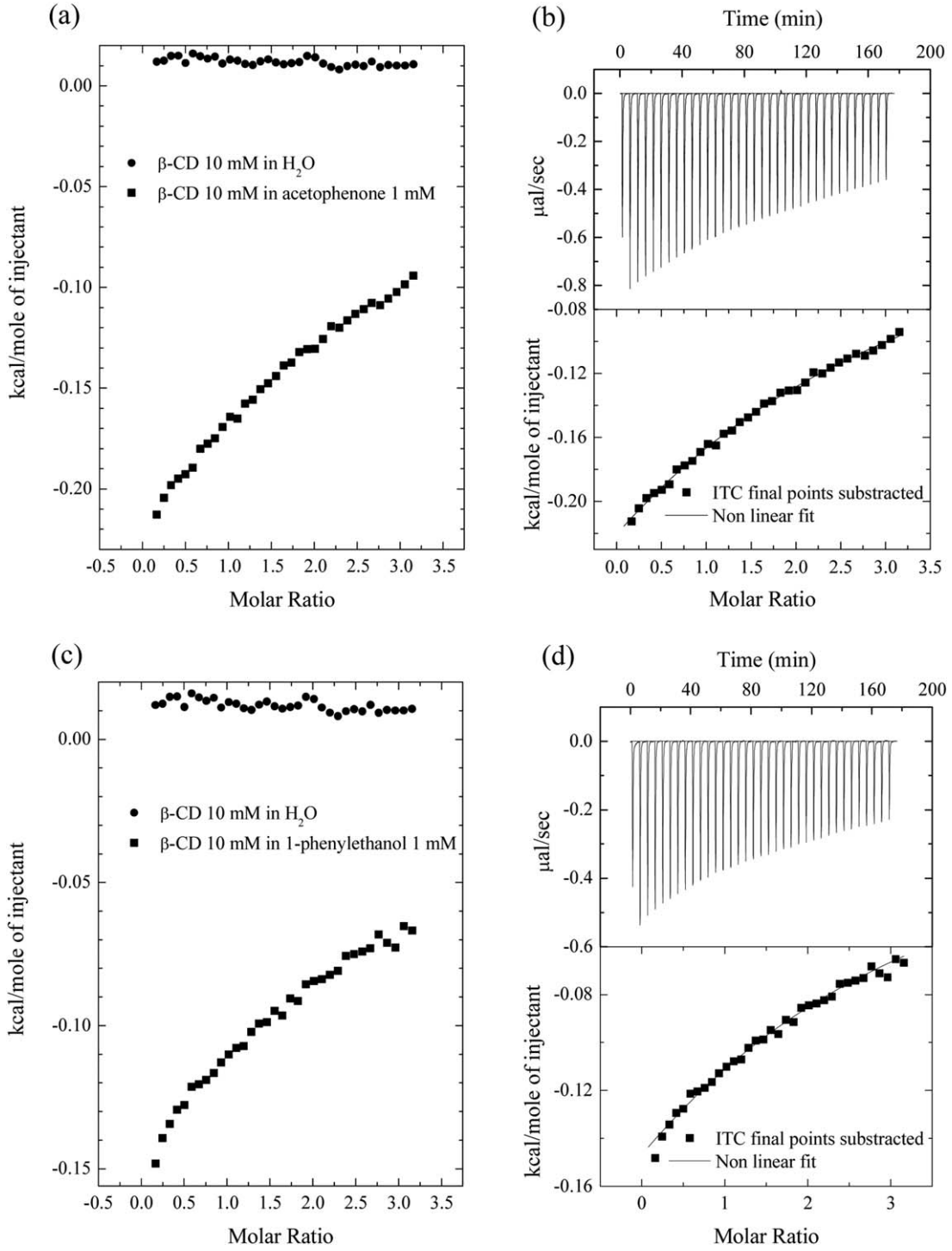

Figure 7. Results of the computer simulation of the ITC titration curve upon formation of the complex at 298 K: (a) heat effects of dilution and complexation of β-CD with acetophenone; (b) final figure for titration of acetophenone with β-CD; (c) heat effects of dilution and complexation of β-CD with 1-phenylethanol; (d) final figure for titration of 1-phenylethanol with β-CD.

Table 3. Thermodynamic Parameters of Interaction Between Guests (Acetophenone and 1-Phenylethanol) and β-CD

Guest	T (K)	K_a (dimensionless)	ΔH (kJ/mol)	ΔS [J/(mol·K)]	ΔG (kJ/mol)
Acetophenone	288	114 ± 4.43	−7.01 ± 0.21	15.25	−11.40
	298	134 ± 3.69	−7.89 ± 0.16	14.41	−12.19
	308	132 ± 5.33	−8.11 ± 0.17	12.26	−11.89
1-Phenylethanol	288	102 ± 5.56	−3.67 ± 0.15	25.83	−11.11
	298	98.4 ± 3.96	−5.42 ± 0.19	16.55	−10.35
	308	79.4 ± 3.34	−6.10 ± 0.21	7.73	−8.48

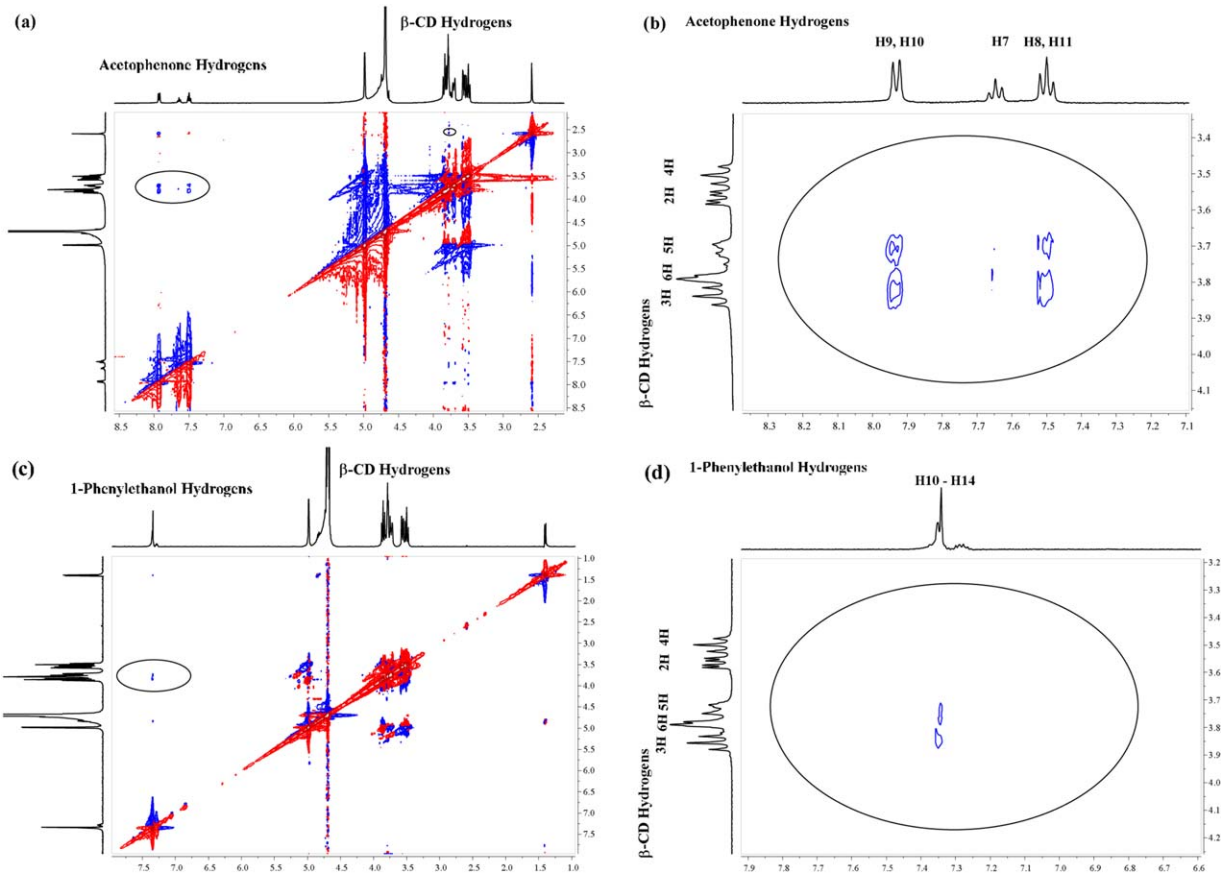

Figure 8. (a) ^{1}H 2D ROESY spectrum of β-CD/acetophenone complex in D_2O at 298 K and (b) expansion of the ROESY spectrum of the acetophenone aromatic region.

(c) ^{1}H 2D ROESY spectrum of β-CD/1-phenylethanol complex in D_2O at 298 K and (d) expansion of the ROESY spectrum of the 1-phenylethanol aromatic region. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Separation of the binary mixture of acetophenone and 1-phenylethanol

Host–guest inclusion complexes are usually formed in aqueous solution, as this maximizes the difference in local polarity between the relatively nonpolar internal cavity of the organic host molecule and the bulk solvent, maximizing the hydrophobic effect as a driving force for inclusion of hydrophobic guests.[48] Therefore, to separate acetopheone and 1-phenylethanol through selective inclusion process by

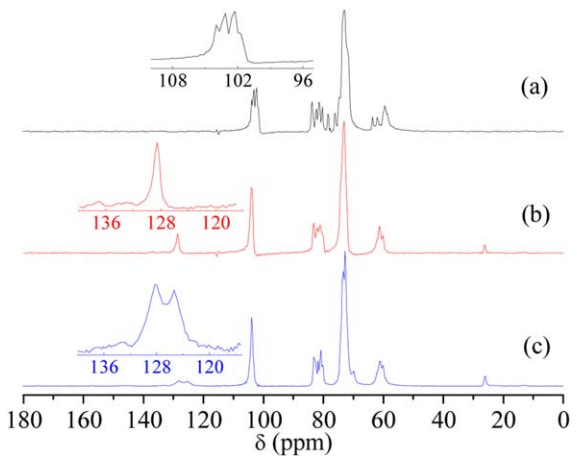

Figure 9. Solid-state ^{13}C CP/MAS NMR spectra of (a) plain β-CD hydrate, (b) β-CD/acetophenone complex, and (c) β-CD/1-phenylethanol complex.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

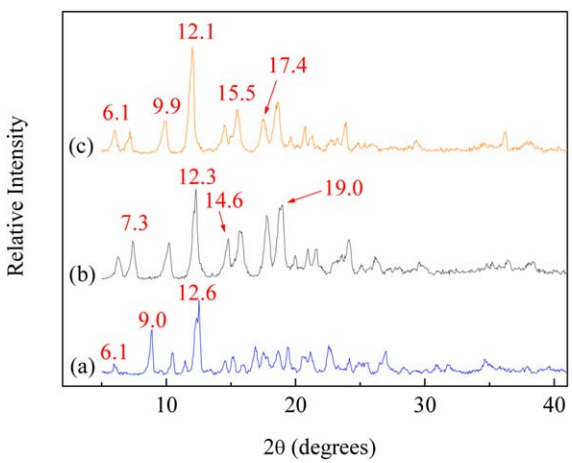

Figure 10. Powder X-ray diffractograms for: (a) β-CD; (b) β-CD/acetophenone inclusion complex; and (c) β-CD/1-phenylethanol inclusion complex.

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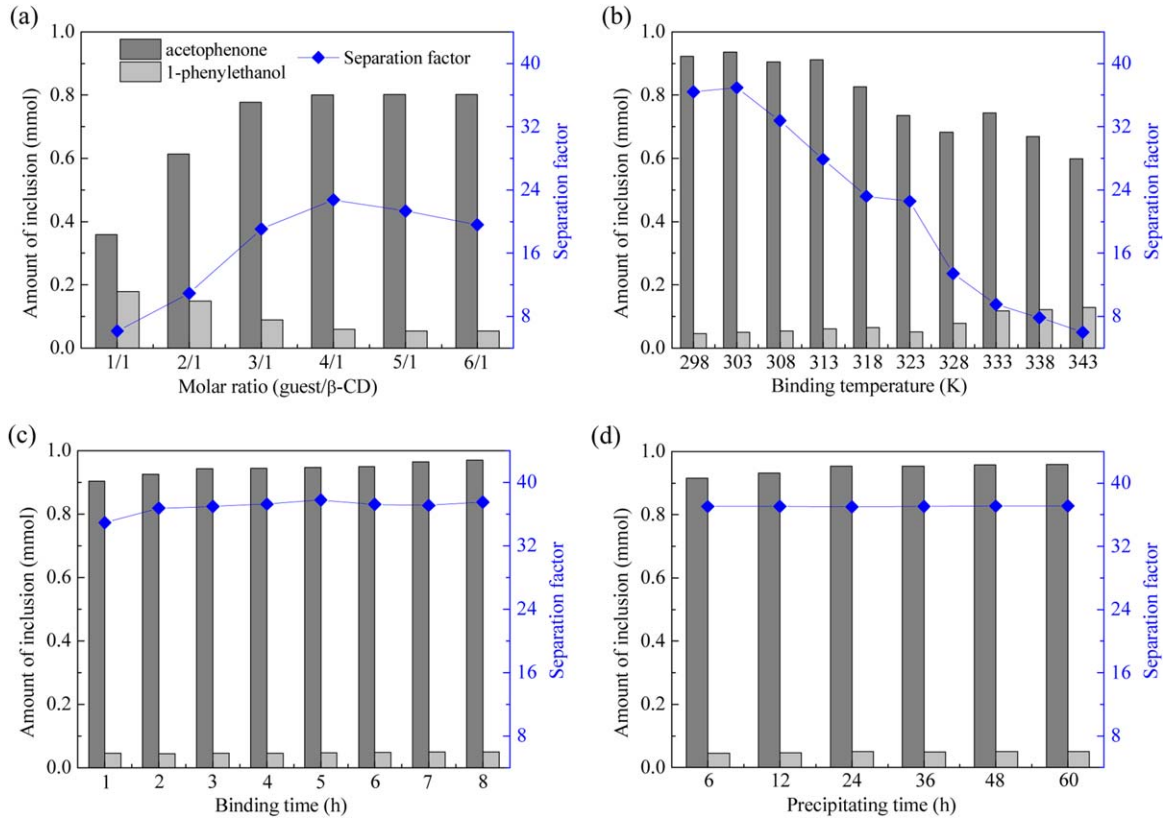

Figure 11. Effects of experimental variables for separation of equimolar mixture of acetophenone and 1-phenylethanol by coprecipitation technique: (a) effect of molar ratio of guest/β-CD, (b) effect of binding temperature, (c) effect of binding time, and (d) effect of precipitating time.

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β-CD, aqueous medium is indispensable for the formation of β-CD complexes. As acetophenone and 1-phenylethanol are slightly soluble in water, white precipitate appeared immediately in the saturated β-CD solution with addition of the mixture, and the contents of guests in both complex and residue changed dramatically. In this study, we call this inclusive separation method "coprecipitation technique."

Using equimolar mixture of acetophenone and 1-phenylethanol, separation efficiency of coprecipitation technique were evaluated under various treatment conditions, including molar ratio of guest/host, binding temperature, binding time, and precipitating time. The results shown in Figures 11a–d indicated that molar ratio of guest/host and binding temperature affect the separation efficiency apparently, while binding temperature and precipitating time do not appreciably influence the host–guest complexation under our experimental conditions. As for the effect of guest/host molar ratio, varying it from 1 to 4, the inclusion amount of acetophenone increased, but 1-phenylethanol decrease simultaneously, so the separation factor increased significantly. It thus suggests that competitive binding behavior exists during the complexation with β-CD between the two guests. However, as the complexes are stoichiometric 1:1 compounds, the amount of the guests in complexes kept stable after the molar ratio reached to be 4, leading to slight decrease of separation factor at higher guest/β-CD molar ratio. Thus, the optimum molar ratio of guest/β-CD can be fixed at 4. While the binding temperature was investigated, the concentration of β-CD in saturated solution changed at the meantime, so the separation efficiency was affected jointly by binding temperature and concentration of β-CD. On the whole, at temperatures above 303 K, an increase of temperature entails a decrease of the inclusion amount of acetophenone and an increase of the inclusion amount of 1-phenylethanol, and the separation factor decreased rapidly (Figure 11b). Therefore, lower temperature is favorable to selective inclusion of acetophenone from the mixture, suggesting that 303 K may be suitable for this inclusive separation technology. From the Figures 11c,d, the effects of binding time and precipitating time were not obvious compared with the former variables, and the optimum binding time and precipitating time can be determined as 2 and 12 h, respectively. In the optimized conditions, it is remarkable that the purity of isolated acetophenone fraction in the complex reaches above 90%. Conversely, the residue becomes impoverished in acetophenone after inclusive separation, resulting in excellent separation efficiency with a separation factor of 37.12.

The molar fractions of acetophenone and 1-phenylethanol in most of the industrial mixtures are different from each other. For this reason, the inclusive separation of binary mixtures with different molar ratios of acetophenone/1-phenylethanol has been performed at the optimum conditions. As shown in Figure 12, through inclusive separation, both the molar fraction of acetophenone in complex and the molar fraction of 1-phenylethanol in residue are higher than the initial molar fraction of acetophenone and 1-phenylethanol for all the mixtures. It also can be seen that the molar fraction of acetophenone can ascend from 80% to 99.2%, especially suitable for preparing acetopheone with high purity from mixture with 1-phenylethanol. Interestingly, both the amount

of acetophenone encapsulated by β-CD and the inclusion selectivity by β-CD are higher than that by α-CD and γ-CD (data not shown). It may be inferred from that the cavity size of β-CD (an inner diameter of 0.78 nm) is large enough to include the guest molecule, whereas the cavity of α-CD or γ-CD (with an inner diameter of 0.57 or 0.95 nm) is too small or too large to sustain the stability of complexes.

Selective inclusion of acetophenone from petrochemical by-product

Five representative experiments for selective inclusion of acetophenone from the petrochemical by-product at different scales were performed, and the experimental results are listed in Table 4. In experiment 1 (abbreviated as Exp. 1), the selective inclusion was conducted in laboratorial bench-scale, and the scale enlarged from bench-scale to 10, 50 times of bench-scale in Exp. 2 and 3, respectively. It can be seen that the mass amount of oil entrapped in 1 g of β-CD is 0.11 g, indicating that the 1:1 complex formation ability of β-CD would be kept in this inclusion process. Conversely, compared with the mass fractions of acetophenone (74.93%) and 1-phenylethanol (17.79%) in the petrochemical by-product, the mass fraction of acetophenone in the complex ($w_{\text{actophenone, c}}$) ascend to 99.24% but the mass fraction of 1-phenylethanol in the complex ($w_{\text{1-phenylethanol, c}}$) drop to 0.75%. It is also worthwhile noted that there was only trace amount of other minor compounds in the complex, although these compounds (2.45 wt % of benzyl alcohol, 0.54 wt % of propylene glycol, 0.31 wt % of styrene, etc.) coexist apparently in the initial oil. The major reason for this is that, β-CD has a much higher affinity and selectivity to acetophenone than to the other compounds in this inclusion process. In addition, it can be seen that the selectivity and capacity of inclusion kept stable during the enlargement of experimental scale. Furthermore, it can be inferred from comparison of the weight of regenerated β-CD and the initial added amount of β-CD that a nearly complete regeneration of β-CD could be obtained by elution with ethyl acetate. Moreover, in the 50× bench-scale inclusion experiment, it is shown that after recycling twice, the amount of the guests included in β-CD still remained nearly constant, indicating the reusability of β-CD.

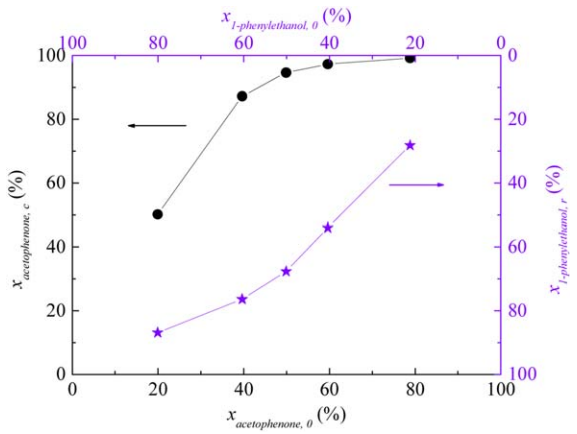

Figure 12. Separation of binary mixtures with different molar fractions of acetophenone and 1-phenylethanol by coprecipitation technique (● stands for molar fraction of acetophenone in complex, ★ stands for molar fraction of 1-phenylethanol in residue).

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 4. Practical Use of β-CD for Selective Inclusion of Acetophenone from Petrochemical By-Product[a]

Experiment No.[b]	Exp. 1	Exp. 2	Exp. 3	Exp. 4	Exp. 5
$m_{\text{CD, 0}}$ (g)	1.00	10.00	50.00	50.00	50.00
$m_{\text{oil, 0}}$ (g)	0.45	4.50	22.50	22.50	22.50
$m_{\text{CD, R}}$ (g)	0.93	9.53	49.29	49.30	49.28
$m_{\text{oil, c}}$ (g)	0.11	1.07	5.33	5.31	5.31
$w_{\text{acetophenone, c}}$ (%)	99.24	99.18	99.13	99.20	99.16
$w_{\text{1-1phenylethanol, c}}$ (%)	0.75	0.80	0.78	0.78	0.77

[a]In each experiment, the other operating conditions are: binding temperature (318 K), binding time (2 h), and precipitation time (12 h).
[b]The scales of Exp. 1–3 are bench-scale, 10× bench-scale and 50× bench-scale orderly. Exp. 4 and 5 are the second and third cycles of 50× bench-scale, respectively.

Conclusions

In this article, inclusive separation of acetophenone and 1-phenylethanol, whose molecular structures and properties are quite similar, was demonstrated resulting from the noncovalent interaction between host (β-CD) and guest (acetophenone and 1-phenylethanol) molecules. Comparison of the value of calculated binding energy from quantum mechanics calculations, equilibrium binding constants and calorimetrically measured thermodynamic parameters between β-CD/acetopheone and β-CD/1-phenylethanol complex indicated that β-CD can bind with acetophenone preferentially to 1-phenyethanol. Confirmation of different intensity of noncovalent intermolecular interactions in complexes was realized according to ^{1}H 2D ROESY and ^{13}C CP/MAS NMR spectra as well as XRD patterns. On the foundation of preferential affinity of β-CD to acetophenone, the coprecipitation technology for separation of acetophenone and 1-phenylethanol has been developed. Although both the guest/host molar ratio and binding temperature play important roles on separation efficiency, the influences of binding time and precipitating time are not very pronounced. Optimization of inclusive separation conditions showed that guest/host molar ratio of 4/1, binding temperature of 303 K, binding time of 2 h, and precipitating time of 12 h were the best conditions for separating acetophenone from 1-phenylethanol. The separation factor α for the equimolar binary mixture of acetophenone and 1-phenylethanol was above 37 under the optimized conditions. By this technique, the molar fraction of acetophenone can ascend from 80% to 99.2%, especially suitable for preparing acetopheone with high purity from mixture with 1-phenylethanol. Interestingly, β-CD showed superior acetophenone/1-phenylethanol selectivity and inclusion ability to α- and γ-CD. Through selective inclusion experiment in 50× bench-scale, it can separate acetophenone from the petrochemical by-product efficiently and economically.

Acknowledgments

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Notation

R = gas constant, 8.314 J/(mol K)
T = temperature, K
$m_{CD,\,0}$ = the added amount of β-CD in the inclusive experiment, g
$m_{oil,\,0}$ = the added amount of petrochemical by-product in the inclusive experiment, g

Subscripts and superscripts

0 = initial condition of experiment
c = inclusion complex
r = residue solution

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